linkers (npeoc, npe and nps) with specific reactions (deprotection reactions), does not provide enablement for any type of protecting groups and deprotection reagents. Applicant respectfully traverses this rejection.

RELEVANT LAW

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of 35 U.S.C. §112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require **undue** experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

It is respectfully submitted that claim 4, and claims 11-16 dependent thereon, are directed to a process for generating a combinatorial library, comprising the steps of preparing a plurality of immobilized molecules selected from a nucleoside and a nucleotide; wherein each molecule contains 3 to 10 reactive moieties, each reactive moiety being blocked by a blocking group, wherein at least three of the blocking groups on each immobilized molecule are independently removable under at least three different conditions; and removing each blocking group and derivatizing the resulting reactive moiety in a preprogrammed, regioselective manner; wherein each member of the plurality of immobilized molecules is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial library.

The Office Action alleges that a number of factors (summarized in the Office Action as factors a) - d)) would prevent one of skill in the art from practicing the claimed subject matter without undue experimentation.

Applicant respectfully disagrees with the specific issues raised in the Office Action as follows:

a) The Office Action alleges that the specification fails to give adequate direction and guidance as to the means of making combinatorial libraries using any type of protecting groups to protect any reactive functional groups using deprotection reagents. It is further alleged that the use of protecting groups and deprotection reagents are specific, and the sequence of deprotection reactions are specific or predetermined based on the stability of the protecting groups.

It is respectfully submitted that a process for generating a combinatorial library is described in the specification in an exemplary embodiment (for example, see specification page 7- 10) wherein oligomers are synthesized for sequence specific selective and orthogonal deprotections and subsequent derivatizations. The exemplary embodiment is illustrated with generalized 5′ to 3′ oligonucleotide synthesis wherein the phosphate protection is achieved by β-

cyanoethyl group, 5'-OH group is protected with dimethoxytrityl group and the bases are protected with nps, npeoc and/or npe protecting groups. The specification, at page 10, lines 1-7, sets forth 16 deprotection combinations to arrive at a combinatorial library. The specification further discusses npeoc/npe base protection on page 12, lines 7-19 and discloses that **other base protecting groups, in addition to the npeoc/npe protection should be suitable for base protection.** The specification page 13, lines 19-21, discusses **stability of acetyl and benzoyl groups in nucleoside base protection during deprotection of phosphate protecting groups.** It is respectfully submitted that base protection in nucleotide/nucleoside synthesis is well documented in the art, and a skilled artisan will be able to use other base protection groups for generation of a combinatorial library as claimed in the instant application with minimal experimentation. Some exemplary references demonstrating the use of various base protection strategies in nucleotide/nucleoside chemistry were provided with the previous response and are further discussed herein.

Furthermore, the specification page 13, lines 7-19, recites various phosphate protecting groups in the following paragraph:

> The phosphate protection with the p-chlorophenyl group e.g. is stable with reagent II in contrast to the β-cyanoethyl group (Hsiung, H.M., *Tetrahedron Lett.,* **1982,** 23, 5119-22). The phosphate protection with the o-chlorophenyl group e.g. is stable with 0.5M hydrazine reagent (Watkins, B.E., Kiely, J. S., Rapoport, H., *J Am. Chem. Soc.,* **1982,** 104, 5702-08). The phosphate protection with the 2,5-dichlorophenyl group e.g. is stable with strong acids as p-toluenesulfonic acid in methylene chloride/methanol (Himmelsbach, F., Schulz, B.S., Trichtinger. T., Ramamurthy, C., Pfleiderer, W,. *Tetrahedron,* **1984,** 40, 59-72). During the deprotection of R^{4B} no removal of the new substituents at ①-④ iis desired. The o-chlorophenyl group e.g. allows deprotection with 4-nitrobenzaldoximate without affecting benzoic acid ester and nps amide bonds (Heikkila, J., Balgobin, N., Chattopadhyaya, J., *Acta Chem. Scand.*, **1983,** B37, 857-62). Further the o-chlorophenyl group e.g. is easily removable with $(n\text{-butyl})_4NF$ (Reese, C.B., Titmas, R.C., Yau, L., *Tetrahedron Lett.,* **1978,** 2727-30). Under these conditions acetic acid ester, trityl ether bonds and the nucleoside base protection with the acetyl or benzoyl groups remain intact (Ogilvie, K.K., *Can.J.Chem.,* **1973,**

51, 3799-3807).

The specification discloses protecting groups for 3' and 5' OH groups on page 15, lines 11-20:

> In addition, if the oligomer (e.g. **3** in scheme 1) is connected at its 3'-OH or 5'-OH group to the CPG via a levulinic acid ester bridge (cleavable with neutral hydrazine reagent IV) instead of the trityl ether bridge in **3**, a simplified 3'-5' as well as 5'-3' directed DNA syntheses would be available, keeping the advantage of multiselective deprotections, with the trityl moiety for easy detection and as a "purification handle" (Sinha, N.D., Biernat, J., Koster, H. *Tetrahedron Lett.,* 1983, 24, 5843-46; Sinha, N.D., Biernat, J., McManus, J., Koster, H. *Nucleic Acids Res.,* **1984,** 12, 4539-57; Sonveaux, E. *Bioorg. Chem.,* **1986,** 14, 274-325). For syntheses by the phosphoamidite method, amidites, whose 5'-OH or 3'-OH groups respectively are protected with the 4,4'-dimethoxytrityl (DMTR) group, are used.

Therefore, the specification discloses stability of various protecting groups under the reaction conditions of orthogonal deprotection and sets forth the criteria for selection of protecting groups and deprotection reagents under reaction conditions of claimed combinatorial libraries. One of skill in the art, based on the teachings of the specification and information available in the art, would know how to select other protecting groups to arrive at a combinatorial library within the scope of the instant claims. Therefore the specification provides adequate direction and guidance to make the combinatorial libraries per the process of instant claims.

b) The Office Action alleges that the working examples are directed to the use of specific protecting groups and deprotection reagents or conditions.

It is respectfully submitted that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. In the above-captioned application, Applicant describes generation of a combinatorial library with exemplary protecting groups for reactive moieties in the molecules on 3'

and 5'-OH, phosphate and nucleoside bases, as discussed above. The reaction conditions of orthogonal deprotection are disclosed explicitly in the specification and the information about various protecting groups is disclosed in the specification and available in the art. Therefore, one of skill in the art can select appropriate protecting groups and deprotection reaction conditions for use in generation of combinatorial library commensurate in scope with the claims.

c) It is alleged in the Office Action that the claims are open ended regarding the use of protecting groups and deprotection reaction conditions, and the order of the deprotection reactions.

Applicant respectfully submits that the claims at issue are directed to a process for generating combinatorial library and one of skill in the art would know that to make a combinatorial library various combinations of protection and deprotection reactions are used. All the possible combinations are contemplated to be within the scope of claims. One cannot prepare a combinatorial library without using a variety of protecting groups. The specification discloses the stability of various protecting groups under the reaction conditions of orthogonal deprotection and sets forth the criteria for selection of protecting groups for reactive moieties in oligonucleotide synthesis. Furthermore, various protecting groups and deprotection reaction conditions used in oligonucleotide synthesis are described in detail in the specification and are known to those of skill in the art, as evidenced by the references cited in the application and listed above.

d) It is alleged that the art is inherently unpredictable because the use of protecting groups in a specific position may be unstable during the deprotection conditions, and result in unwanted reactions occuring.

Applicant respectfully submits that the use of various protecting groups and deprotection reagents is well known in the art of nucleotide/nucleoside chemistry, as demonstrated by several articles discussed herein. Applicant agrees that the use of a protecting group in a specific position may be unstable

during the deprotection conditions, but it is respectfully submitted that based on his/her knowledge and skill, one of skill in the art would know which protecting groups are suitable for use under a particular reaction condition because the use of protecting groups is well documented in the art and the specification discloses exemplary protecting groups and deprotection conditions. Therefore, based on the information provided in the application and knowledge available in the art, a skilled artisan would be able to choose appropriate protecting groups and deprotection reagents.

Response to Arguments

The Office Action makes several arguments in response to Applicant's remarks in the previous response. It appears that Examiner's rejection is based on the allegation that the specification and the art of record refer to only the use of npe/npeoc protecting groups. Applicant strongly disagrees. In addition to npe/npeoc, the specification discloses the use of several other protecting groups, including but not limited to, nps, chlorophenyl, β-cyanoethyl, levulinic acid ester and DMTr. Furthermore, the art of record refers to a multitude of protecting groups, including but not limited to, benzoyl, 4-methoxybenzoyl, pivaloyloxymethyl, allyloxycarbonyl, dialkylformamidine, benzoylpropionyl, 5-pentenoyl, isobutyryl and Fmoc group. Therefore, the specification and state of the art provides numerous protecting groups for use in the claimed processes.

The Office Action alleges that the specification pages 11, and 14-20 referred in Applicants previous response specifically only teach the use of "npe" and "npeoc" as protection groups.

Applicant respectfully disagrees. Applicant draws Examiner's attention to the fact that pages 11 and 14-20 of the specification were referred to in Applicants previous response in support of the argument that all the steps in the claimed method are described in the specification. Furthermore, pages 11 and 14-20 of the specification teach the use of several protecting groups, including but not limited to, nps, chlorophenyl, β-cyanoethyl, levulinic acid ester and

DMTr. For example, the specification at page 14, line 1-13 recites the use of nps protecting group:

> The rate of base deprotection in nps base protected nucleosides was found to be significantly influenced by the deprotection reagent (thiocresolate concentration and solvents). The rate of deprotection in 0.02M thiocresolate in pyridine decreases as follows: 2'-deoxy-N^2-nps-guanosine (G_d^{nps}) > > 2'-deoxy-N^4-nps-cytidine (C_d^{nps}) > > 2'-deoxy-N^6-nps-adenosine (A_d^{nps}). It would seem to be difficult to identify reagents leading to a reversion of this order to obtain e.g. nps protected cytosine and guanine in the presence of nps deprotected adenine moieties. But such a deprotection state could be achieved by selective deprotection of the C^{nps} and G^{nps} moieties, followed by reprotecting them with groups, stable with thiocresolate reagent. Finally A^{nps} can be deprotected with this reagent. In yet another approach, this protection scheme can be obtained by using the suitably protected nucleotide building blocks during oligomer synthesis.

The specification at page 14, line 23 through page 15, line 8 recites the use of chlorophenyl, β-cyanoethyl, levulinic acid ester and nps groups:

> For the phosphtriester method, chloro substituted phenyl groups and the ß-cyanoethyl group were successfully used as phosphate protection groups (Amarnath, V., Broom, A. D. *Chem. Rev.* **1977**, 77, 183-217; Reese, C. B., *Tetrahedron,* **1978,** 34, 3143-79). The levulinic acid ester and the npeoc/npe base protection are stable during the reaction conditions of the phosphotriester method (Himmelsbach, F., Schulz, B.S., Trichtinger, T., Ramamurthy, C., Pfleiderer, W., *Tetrahedron,* **1984,** 40, 59-72; van Boom, J.H., Burgers, P.M.J., *Tetrahedron Lett.,* **1976,** 4875-78). The nps base protection has been successfully used during the oligonucleotide synthesis by the phosphotriester approach (Heikkila, J., Balgobin, N., Chattopadhyaya. J., *Acad Chem. Sci.,* **1983,** B37, 857-62).

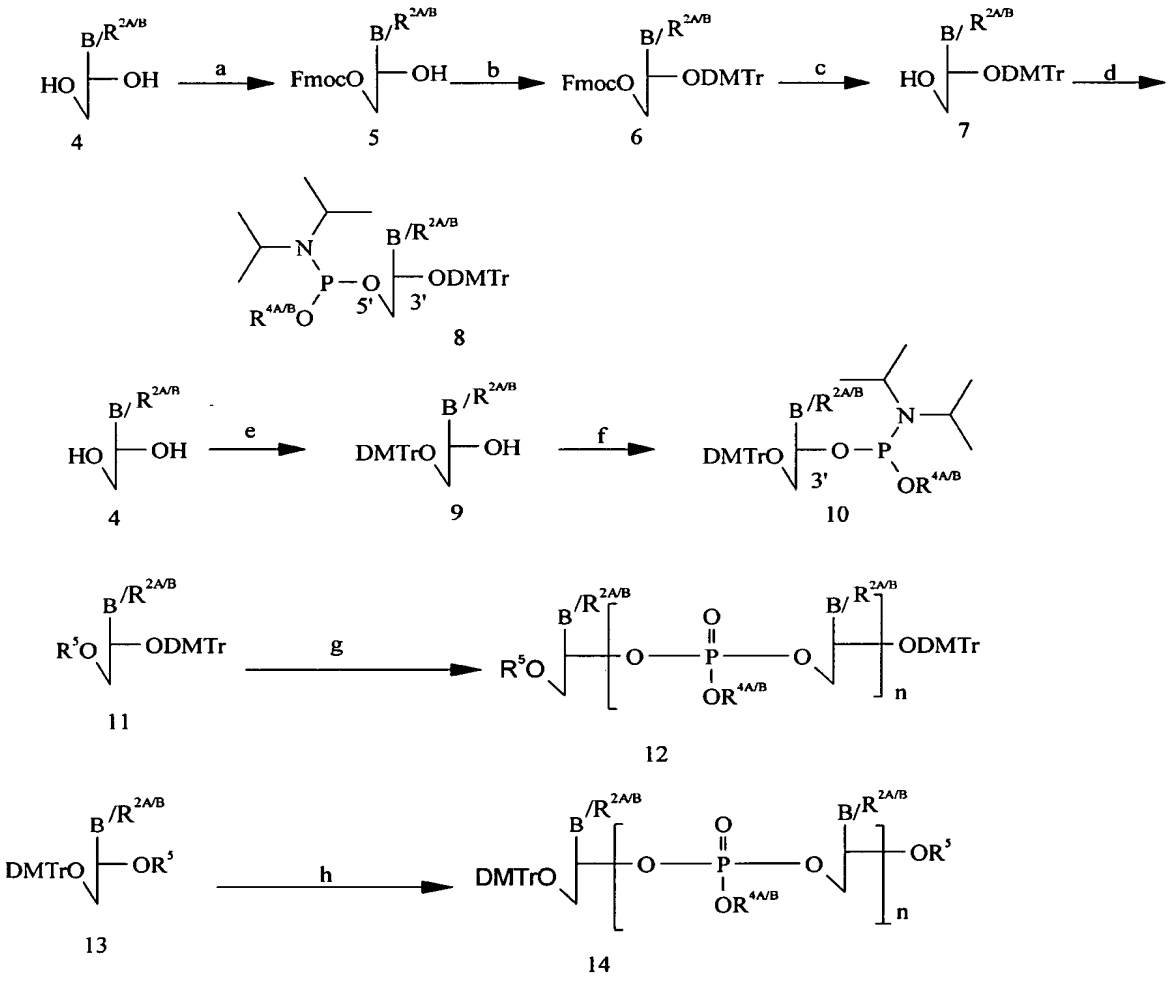
The specification at page 15, lines 11-20, further discloses the use of levulinic acid ester and DMTr groups:

> In addition, if the oligomer (e.g. **3** in scheme 1) is connected at its 3'-OH or 5'-OH group to the CPG via a levulinic acid ester bridge (cleavable with neutral hydrazine reagent IV) instead of the trityl ether bridge in **3,** a simplified 3'-5' as well as 5'-3' directed DNA syntheses would be available, keeping the advantage of multiselective deprotections, with the trityl moiety for easy detection and as a "purification handle" (Sinha, N.D., Biernat, J., Koster, H. *Tetrahedron Lett.,* 1983, 24, 5843-46; Sinha, N.D., Biernat, J., McManus, J., Koster, H. *Nucleic Acids Res.,*

1984, 12, 4539-57; Sonveaux, E. *Bioorg. Chem.,* **1986,** 14, 274-325). For syntheses by the phosphoamidite method, amidites, whose 5'-OH or 3'-OH groups respectively are protected with the 4,4'-dimethoxytrityl (DMTR) group, are used.

Reaction scheme 3 on page 16, and reproduced below, discloses the use of Fmoc and DMTr protecting groups for 5' and 3'-OH groups.

SCHEME 3



a: selective 5'-OH protection. b: tritylation with DMTr chloride. c: 5'-OH deprotection, e.g. with *tert*-butyl amine reagent II (table 1) or with triethyl amine reagent. d: phosphitylation. e: selective 5'-OH protection with DMTr chloride. f: phosphitylation. g: 5'-3' directed oligonucleotide synthesis with **11** and **8.** h: 3'-5' directed oligonucleotide synthesis with **13** and **10** R^5: CPG----- $CH_2COCH_2CH_2CO$-(support anchored levulinyl group); n, B, B^R, $B^{R2A/B}1$, $R^{4A/B}$, $R^{4A/B}$: see Scheme 1.

The specification at page 18, line 14, through page 19, line 10, discusses stability of nps protecting group:

> The following findings demonstrate the feasibility of this extension of the synthetic strategy with the levulinic acid ester bridge. The base protection of nucleosides protected with the 2-nitrophenylsulfenyl (nps) group is rather stable with strongly acidic solutions (Heikkila, J., Balgobin, N., Chattopadhyaya, J., *Acta Chem. Scand,* **1983,** B37, 857-62). We found that stability against depurination in 80% acetic acid decreases as follows: 2'deoxy-N^6-nps-adenosine (A_d^{nps}) >> 2'-deoxy-N^2-nps-guanosine (G_d^{nps}) > 2'-deoxy-N^2isobutyryl-guanosine (G_d^{ib}) >> 2'-deoxy-N^6-benzoyl-adenosine (A_d^{bz}); G_d^{ib} and A_d^{bz} are exposed to strong acids in every elongation cycle in the standard DNA synthesis process (Sinha, N.D., Biernat, J., Koster, H., *Tetrahedron Lett.,* **1983,** 24, 5843-46; Sinha, N.D., Biernat, J., McManus, J., Koster, H., *Nucleic Acids Res.,* **1984,** 12, 4539-57; Sonveaux, E., *Bioorg. Chem.,* **1986** 14, 274-325). In accordance with Heikkila, J. et al. *(Acta Chem.Scand.,* **1983,** B37, 857-62). A_d^{nps} does not depurinate with 80% acetic acid, although the

> main depurination problem in standard DNA synthesis is caused by the A_d^{bz} units. 2'-Deoxy-N^4-nps-cytidine (C_d^{nps}) is stable with 80% acetic acid.

Therefore the allegation in the Office Action that pages 11 and 14-20 of the specification, referred to in Applicant's previous response specifically only teach the use of "npe" and "npeoc" protecting groups is incorrect. As discussed above, the use of several other protecting groups is taught in the specification at pages 11 and 14-20.

The Office Action further urges that Applicant's arguments that various blocking groups for the reactive moieties in the molecules on phosphate and nucleoside bases are well characterized in the instant application and are well known to those with skill in the art, as are the deprotecting reagents for selective orthogonal deprotection (see pages 12-13), are not persuasive. The Office Action notes that the specification on page 12 discloses that npeoc/npe protection is found to be stable during deprotection conditions. It is further noted in the Office Action that page 13 of the specification discloses different protecting groups useful in protecting the phosphate group. It is alleged in the Office Action that all the reactive moieties in the claimed methods are not the phosphate groups as stated in the applicants arguments.

Applicant respectfully submits that the Office Action has mischaracterized Applicant's remarks. Applicant has never stated or indicated in the previous response that "all the reactive moieties in the claimed methods are the phosphate groups." Applicant's previous response on page 19, lines 5-8, recites:

> various blocking groups for the reactive moieties in the molecules on **phosphate and nucleoside bases** are well characterized in the instant application and are well known to those with skill in the art, as are the deprotecting reagents for selective orthogonal deprotection (see pages 12-13)".

Therefore the reference in the previous response was to the protecting

groups and deprotecting conditions for **nucleotide bases and phosphate groups.** Furthermore, as discussed above, the specification also discloses protecting groups for nucleoside bases and 3' and 5'-OH groups.

It is further alleged in the Office Action that the specification disclosure and several papers cited in the previous response refer to only the use of npe/npeoc protecting groups in multi selective deprotection methods as claimed.

Applicant disagrees. As discussed above the specification discloses protecting groups other than npe and npeoc, including but not limited to base protecting groups such as nps (specification page 13, line 22 through page 14 line 11), acetyl and benzoyl groups (specification page 13, lines 19-21); various phosphate protecting groups including, p-chlorophenyl, 2,5-dichlorophenyl, o-chlorophenyl (specification page 13, lines 7-21); protection of 3'-OH and 5'-OH groups with Fmoc (specification page 16, reaction scheme 3), dimethoxytrityl and levulinic acid ester group (specification page 9, lines 6-14 and page 15, lines 11-20). Several papers cited in the previous response disclose numerous protecting groups other than npe and npeoc, including but not limited to, benzoyl, 4-methoxybenzoyl, pivaloyloxymethyl, allyloxycarbonyl, dialkylformamidine, benzoylpropionyl, 5-pentenoyl, isobutyryl and Fmoc group, as discussed below:

The protection of the carbohydrate 5' and/or 3'- hydroxy functions with protecting groups, including but not limited to, **trityl, acetyl, benzoylpropanoyl;** phosphate protection with **β-cyanoethyl, chlorophenyl;** and protection of the amino function on bases with **dimethylaminomethylene, acyl** is discussed in extensive details in the article published by Amarnath *et al.*, Chemical Reviews, **1977**, 77, 183-217. The protecting groups are categorized as acid labile, base labile and groups removable under neutral conditions. The reference describes reagents and conditions for deprotection of the protecting groups, for example 2,4-dinitrobenzenesulfenyl protecting group on 5'-hydroxy site of nucleosides can be removed by thiophenol in phenol.

An extensive review published by E. Sonveaux, *Bioorg. Chem.,* **1986,** 14, 274-325, discusses several protecting groups, including but not limited to, various **acyl groups, DmTr and pixyl,** for use in different oligonucleotide synthesis methods for individual bases and for 3'- and 5'-hydroxy groups.

An article by Reese, C. B., *Tetrahedron,* **1978,** 34, 3143-79, reviews various protecting groups, including but not limited to **benzoyl, p-anisoyl** for -OH functionalities and for the bases.

Watkins *et al.* in *J Am. Chem. Soc.,* **1982,** 104, 5702-08, have described use of **benzyloxycarbonyl** group removable under neutral hydrogenolysis conditions for base protection in oligonucleotide synthesis.

Gioeli *et al.* in *J. Chem. Soc. Chem. Commun.,* **1982,** 672-74, have described **Fmoc group** removable by basic reagents such as aqueous ammonia, piperidine, ethanolamine or morpholine, in the 5'-*O*-Fmoc-2'-deoxythymidine having orthogonal deprotection properties described in the instant application.

Kharasch *et al. J. Amer. Chem. Soc.,* **1953,** 75, 2658-60, have described **2,4-dinitrophenylsulfenyl (dnps) group** in the dnps ethyl ester which reveals selective deprotection properties with deprotection reagents described in the instant application.

Several articles cited in the application on page 13 disclose phosphate and base protection groups and deprotection reagents.

In addition, a large body of publications, not cited in the application, describe protecting groups for nucleoside bases. Some exemplary publications are listed below.

U.S. Patent Nos. 5,763,599 and 5,652,358, describe **phenoxyacetyl, benzoyl, isobutyroyl, p-(t-butyl)benzoyl and p-(t-butyl)phenylacetyl** protecting group for nucleotide bases.

Koster et al., Tetrahedron 37, 363-369, and Ti *et al.* J. Am. Chem. Soc. 1982, 104: 1316-1319, report several **acyl protecting groups** for use in oligonucleotide synthesis. Comparative rates of deacylation of various acyl

protecting groups in MeOH/NaOH mixture are also reported.

Rasmussen *et al.* J. Am. Chem. Soc. 1967, 89(21): 5439-45, disclose **pivaloyloxymethyl protecting group** removable under mildly basic conditions, for adenine.

Hayakawa *et al.* J. Am. Chem. Soc. 1990, 112: 1691-1696, describe **allyloxycarbonyl (AOC) protecting group** for nucleoside bases. AOC group can be removed by palladium(O) catalyzed reaction under mild conditions.

Vu *et al.* Tetrahedron Letters, 1990, 31, 7269-7272, describe **dialkylformamidine and isobutyryl** protection of nucleosides. Deprotection can be achieved under mild basic conditions.

Dreef-Tromp *et al.* Tetrahedron Letters, 1990, 31, 427-430, describe **2-(*tert*-butyldiphenylsilyloxymethyl)benzoyl protecting group** removable under neutral conditions by fluoride ion.

U.S. Patent No. 5,614,622 describe the use of **5-Pentenoyl** moiety as nucleoside amino protecting group in oligonucleotide synthesis. It can be deprotected by chemoselective removing agents for example, halogens in water or pyridine/alcohol or by nonchemoselective removing agents such as aqueous ammonium hydroxide or alcoholic ammonia.

Caruthers *et al.* Nucleosides & Nucleotides, 4(1&2), 95-105, have described various **amidine protecting groups** which can be removed under basic condition, for nucleoside bases.

Letsinger *et al.* J. Am. Chem. Soc. 1969, 91:12: 3356-59, describe **β-benzoylpropionyl and benzoylformyl** for -OH protection of nucleosides and **isobutyloxycarbonyl** for $-NH_2$ protection during oligonucleotide synthesis. These can be removed under neutral conditions.

Vinogradov *et al.* Tetrahedron Letters 1993, 34, 5899-5902, describe **isopropoxyacetal group** for the protection of the exocyclic amine of the nucleic bases. Deprotection was achieved under basic conditions.

Kamimura *et al.* Tetrahedron Letters 1983, 24, 2775-2778, reported

diphenylcarbamoyl group for protection of 6-O and **propionyl group** for protection on amino group in guanine. It was removed by ammonia + pyridine.

McBride *et al.* Tetrahedron Letters 1983, 24, 2953-56, reported **N-methyl-2-Pyrrolidine amidine** group as deoxynucleoside protecting group and removal was achieved by ethylenediamine:phenol.

Ogilvie *et al.* Tetrahedron Letters 1982, 23, 2615-18, describe **Levulinyl group** for amino protection in nucleosides and hydrazine as deprotection reagent.

Froehler *et al.* Nucleic Acid Research 1983, 11, have reported **dialkylformamidine protecting group** removable with ammonia, for N protection in deoxyadenosine.

Therefore the cited articles disclose the use of several protecting groups other than npe and npeoc.

The Office Action further alleges that Applicant's argument in the previous response, that the skilled artisan knew various protecting groups and deprotection reagents and conditions for use in nucleotide/nucleoside synthesis at the time of the effective filing date of this application and before, is not persuasive, because the instant claimed method is not just nucleoside/ nucleotide synthesis. It is further stated that the claimed method requires that each immobilized molecule(oligonucleotide) contains 3-10 reactive moieties, each reactive moiety is being blocked by a blocking group, wherein at least three of the blocking groups on each immobilized molecule are independently removable under at least three different reaction conditions. It is further noted that the blocking groups have to be stable at various deprotection conditions. The Office Action alleges that the specification disclosure is based on the use of specific blocking groups and does not give guidance for using or selecting any other known blocking groups in the selective deblocking conditions of the claimed method.

Applicant respectfully submits that as discussed above, the instant claims

are directed towards preparation of a combinatorial library of nucleotides/nucleosides comprising the steps of preparing a plurality of immobilized molecules selected from a nucleoside and a nucleotide; wherein each molecule contains 3 to 10 reactive moieties, each reactive moiety being blocked by a blocking group, wherein at least three of the blocking groups on each immobilized molecule are independently removable under at least three different conditions; and removing each blocking group and derivatizing the resulting reactive moiety in a preprogrammed, regioselective manner; wherein each member of the plurality of immobilized molecules is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial library.

The specification describes the use of various protecting groups in the claimed process, including but not limited to base protecting groups such as npe, npeoc (specification pages 7 and 8), nps (specification page 13, line 22 through page 14 line 11), acetyl and benzoyl groups (specification page 13, lines 19-21); phosphate protecting groups including, p-chlorophenyl, 2,5-dichlorophenyl, o-chlorophenyl (specification on page 13, lines 7-21); 3'-OH and 5'-OH protecting groups Fmoc (specification page 16, reaction scheme 3), dimethoxytrityl and levulinic acid ester group (specification page 9, lines 6-14 and page 15, lines 11-20). The specification describes, in an exemplary embodiment, the use of deprotecting reagents to deblock the blocking groups under selective and orthogonal conditions. For example, see specification page 9, lines 15-27:

Table 1. Selective and orthogonal deprotection at oligomer 3.

Deprotection at linkage in 3	*Reaction*	*Deprotection reagent*
①	detritylation I:	80% acetic acid
②	decyanoethylation II:	tertbutyl amine/ pyridine 1/9 (v/v)
③	base deprotection III:	p-thiocresole in

			pyridine/DMF 3/7 (v/v): 3mmol/ ml
④	hydrazinolysis	IVa:	IM hydrazinium hydrate in pyridine/ glacial acetic acid/ water (4:3:0.35, v/v), pH 5.4
		IVb:	0.5M hydrazinium hydrate in pyridine/ glacial acetic acid/ water (4:1:0.25, v/v), pH 6.5

As discussed above, there is a wealth of information available in the art about protecting groups and deprotection conditions, for example, "Protecting Groups in Organic Synthesis" by T. W. Greene, describes several protecting groups used in organic synthesis. Based on the disclosure of the instant specification and the information available in the art regarding protection/deprotection chemistry, a skilled artisan would be able to select at least three different protecting groups removable under at least three different conditions for use in the claimed process. For example, 3' and 5'-OH protection by a pixyl group (removed under acidic conditions), base protection with bezyloxycarbonyl group (removed under reductive conditions) and phosphate protection with o-chlorophenyl group (removed with $(n\text{-butyl})_4NF$)) represent one possible set of protecting groups removable under selective and orthogonal conditions. Therefore, it is respectfully submitted that the disclosure of the specification combined with the information available in the art, one of skill in the art would be able to choose three different protecting groups for use in the claimed method.

The Office Action further alleges that all the articles referred by Applicant are based on the method wherein individual blocking group and one deblocking conditions are used. Applicant respectfully submits that it is the subject matter of the instant application to select a set of at least three different blocking groups independently removable under at least three different conditions to generate a combinatorial library. The art is referred to demonstrate the

multitude of information available about protecting groups used to block reactive moieties in organic synthesis and deprotection conditions used to remove the protecting groups, based on which a skilled artisan would be able to select at least three protecting groups removable under at least three different deprotecting conditions. Protection/deprotection of reactive moieties is routinely practiced in organic synthesis. The level of skill in the field is very high. A skilled artisan would be able to make a choice of appropriate protecting groups/deprotection conditions based on the information about selective and orthogonal deprotection disclosed in the specification and available in the art for use in the instantly claimed methods. Therefore, it is respectfully submitted that the disclosure of the specification, in view of the information available in the art, does enable one of skill in the art to practice the full scope of the claimed processes.

* * *

In view of the remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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